dues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
19. A detailed explanation of PolyPhen scoring criteria is available at http://tux.embl-heidelberg.de/ramensky/doc/pph_help.html.
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**Supporting Online Material**
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# HLA and NK Cell Inhibitory Receptor Genes in Resolving Hepatitis C Virus Infection

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Natural killer (NK) cells provide a central defense against viral infection by using inhibitory and activation receptors for major histocompatibility complex class I molecules as a means of controlling their activity. We show that genes encoding the inhibitory NK cell receptor KIR2DL3 and its human leukocyte antigen C group1 (HLA-C1) ligand directly influence resolution of hepatitis C virus (HCV) infection. This effect was observed in Caucasians and African Americans with expected low infectious doses of HCV but not in those with high-dose exposure, in whom the innate immune response is likely overwhelmed. The data strongly suggest that inhibitory NK cell interactions are important in determining antiviral immunity and that diminished inhibitory responses confer protection against HCV.

Natural killer (NK) cells are key components of the innate antiviral immune response. In vivo, they are under the constitutively dominant influence of inhibitory receptors for self-MHC class I ligands (*1*, *2*), such that effector functions occur only when activating signals overcome inhibitory signals (*3*, *4*). The killer cell immunoglobulin-like receptors (KIR) represent a diverse family of activating and inhibitory receptors that are integral in this model. As with their MHC class I ligands, the population diversity and rapid evolution of the *KIR* genes strongly suggests that they are under pathogen-mediated selection (*5*–*7*).

*KIR* haplotypes vary in number and type of genes present, and because *HLA* and *KIR* map to separate chromosomes, some individuals lack specific KIR-HLA receptor-ligand pairings. To date, only activating *KIR* have been associated with disease outcome (*8*–*10*), whereas the influence of inhibitory *KIR* on disease is undetermined.

Hepatitis C virus (HCV) is a common infection worldwide, causing cirrhosis and hepatocellular carcinoma. About 20% of individuals resolve acute infection, an outcome associated with specific components of the adaptive immune system (*11*), including *HLA* class I (*12*). Because resolution of HCV infection may also involve the innate immune system, including NK cells (*13*, *14*), we examined the possible synergistic influence that corresponding *KIR-HLA* combinations might have on the outcome of HCV infection.

Individuals who were exposed to HCV (685 with persistent and 352 with resolved infection) (table S1, A to C) were categorized according to their KIR-binding motifs based on *HLA-B* and *-C* genotyping data (*15*). Group 1 HLA-C (HLA-C1) allotypes have asparagine at residue 80 and are ligands for the inhibitory receptors KIR2DL2 and KIR2DL3, which segregate as alleles of a single locus (Table 1). The remaining HLA-C allotypes (group 2, HLA-C2) have

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**Table 1.** Frequency of KIR and HLA receptor-ligand pairings in the population studied, stratified by race, study site, and route of infection.

| | *N* | *KIR2DL1-HLA-C2* *N* (%) | *KIR2DL2-HLA-C1* *N* (%) | *KIR2DL3-HLA-C1* *N* (%) | *KIR2DS1-HLA-C2* *N* (%) | *KIR2DS2-HLA-C1** *N* (%) | *KIR3DL1-HLA-Bw4* *N* (%) | *KIR3DS1-HLA-Bw4** *N* (%) |
|---|---|---|---|---|---|---|---|---|
| All | 1037 | 689 (66.4) | 591 (57.0) | 754 (72.7) | 231 (22.3) | 441 (42.5) | 635 (61.2) | 216 (20.8) |
| | | | | *Race*† | | | | |
| UK Caucasian | 340 | 219 (64.4) | 144 (42.4) | 271 (79.7) | 78 (22.9) | 144 (42.3) | 205 (60.1) | 83 (24.4) |
| USA Caucasian | 355 | 220 (62.0) | 163 (45.9) | 265 (74.6) | 88 (24.8) | 167 (47.0) | 205 (57.7) | 89 (25.1) |
| USA African-American | 271 | 205 (75.6) | 108 (39.9) | 166 (61.3) | 47 (17.3) | 99 (36.5) | 188 (69.4) | 31 (11.4) |
| USA other | 69 | 44 (63.8) | 30 (43.5) | 52 (75.4) | 17 (24.6) | 30 (43.5) | 35 (50.7) | 12 (17.4) |
| | | | | *Route* | | | | |
| No blood products | 543 | 372 (68.5) | 229 (42.2) | 382 (70.3) | 115 (21.2) | 222 (40.9) | 344 (63.3) | 105 (19.3) |
| Blood products | 494 | 317 (64.2) | 217 (43.9) | 372 (75.3) | 116 (23.5) | 219 (44.3) | 291 (59.0) | 111 (22.5) |

*Receptor ligand pairing inferred by protein sequence but not directly demonstrated. †Excludes two non-Caucasian individuals from the United Kingdom.

lysine at position 80 and are ligands for KIR2DL1 (an inhibitory receptor) and KIR2DS1 (the homologous activating receptor). HLA-B Bw4 allotypes serve as ligands for KIR3DL1.

The frequency of individuals with two copies of *HLA-C1* alleles (*HLA-C1C1*) was higher in the group that had resolved infection (37.5%) relative to those with persistent infection (29.9%) ($P = 0.01$; OR = 1.40). The reciprocal association of two *HLA-C2* alleles (*HLA-C2C2*) with viral persistence (14.5% in resolved versus 20.2% in persistent infection) was also observed ($P = 0.02$; OR = 0.67) (Table 2). The frequency of *HLA-B Bw4* alleles did not differ significantly between the groups.

Although both KIR2DL3 and KIR2DL2 bind HLA-C1 allotypes, KIR2DL2 binds HLA-C1 with greater affinity than does KIR2DL3 (*16*). We hypothesized that a weaker inhibitory receptor-ligand (KIR2DL3-HLA-C1) interaction would be protective, because it should be more easily overridden by activating signals than a stronger inhibitory interaction such as KIR2DL2-HLA-C1 or KIR2DL1-HLA-C2. Consistent with this model, the protective association of *HLA-C1C1* was significant only among individuals homozygous for *KIR2DL3* ($P = 0.003$; OR = 1.71) and not among *KIR2DL2/KIR2DL3* heterozygotes or *KIR2DL2* homozygotes (Table 2). Thus, the presence of *KIR2DL2* appears to counteract *KIR2DL3-HLA-C1C1* protection. Further, *KIR2DL3* did not associate with HCV resolution in individuals who were lacking *HLA-C1C1*, which indicates a synergistic protective effect between *HLA-C1C1* and *KIR2DL3/KIR2DL3*, as opposed to additive, independent effects of each. All individuals in this study have at least one copy of *KIR2DL1*, so it was not possible to determine whether the susceptible *HLA-C2C2* effect is independent of *KIR2DL1*. Neither *KIR2DS2* nor *KIR2DS1*, activating receptors with high sequence similarity to *KIR2DL2/KIR2DL3* and *KIR2DL1*, respectively, were associated with HCV resolution, but *KIR3DS1* displayed a weak protective effect in combination with *HLA-B Bw4+* alleles ($P = 0.04$; OR = 1.39).

Resistance to murine cytomegalovirus infection is dependent on the NK cell receptor Ly49H (*17*) and can be overcome by increasing the size of the infecting inoculum (*18*). To investigate whether a similar dose-response relation could be detected with HCV infection, individuals were stratified by the expected inoculum size, assuming that individuals who contract HCV by transfusion of either blood or concentrated blood products ($N = 494$) receive larger inocula than those infected by injection drug use and needle-stick injuries (nontransfused) ($N = 543$) (table S1B) (*19*, *20*).

Among nontransfused individuals, 20.4% of those resolving infection had the compound genotype *KIR2DL3/KIR2DL3-HLA-C1C1*, as compared with 9.9% with persistent infection ($P = 0.001$; OR = 2.33) (Table 3). Further, homozygosity for *HLA-C1* was protective only among individuals who were homozygous for *KIR2DL3* ($P = 0.0001$; OR = 3.01) but not in those with one or no *KIR2DL3* genes ($P = 0.6$ and $P = 0.3$, respectively) (Table 4). Protection conferred by *KIR2DL3/KIR2DL3-HLA-C1C1* was stronger than any other *KIR-HLA* combination tested, indicating a direct, primary effect of this genotype on HCV clearance (tables S2 and S3). Alternatively, *KIR2DL3/KIR2DL3-HLA-C1C1* showed no protection among transfused individuals.

*KIR2DL3/KIR2DL3-HLA-C1C1* protection was observed in both nontransfused Caucasians and African Americans. Among Caucasians homozygous for *KIR2DL3* ($N = 145$), 21.7% of persistently infected versus 49.1% of resolved individuals were *HLA-C1C1* ($P = 0.0009$; OR = 3.47), as compared with 20.6% versus 36.4%, respectively, in African Americans ($N = 106$; $P = 0.096$; OR = 2.21). Although the protective effect did not reach significance in African Americans, the consistent trends across racial groups further suggest that a synergistic interaction between *KIR2DL3* and *HLA-C1* directly confers protection against HCV, rather than indirectly through linkage disequilibrium with neighboring loci.

Multiple variable logistic regression analyses of variables that were significant ($p < 0.05$) in univariate analysis supported a protective effect of *HLA-C1C1* only in the context of *KIR2DL3* homozygosity and only among nontransfused individuals ($P = 0.001$; OR = 2.24) (Table 5). Conversely, the adverse effect of *HLA-C2C2* alone and in combination with *KIR2DL1* was no longer significant, suggesting that its effect in univariate analysis derives from the absence of protective *HLA-C1* alleles. The weak effect of *KIR3DS1-Bw4* persisted, ap-

**Table 2.** *HLA-C* and *KIR-HLA-C* interactions are associated with resolution of HCV infection. Frequencies of *HLA-C* and *KIR-HLA-C* combinations among individuals with resolved and persistent HCV infection from all individuals combined are shown. *HLA-C1C1* indicates two group 1 *HLA-C* alleles, *HLA-C2C2* indicates two group 2 *HLA-C* alleles, and *HLA-C1C2* indicates one of each. *P* values were calculated by using the chi-square test from two-by-two contingency tables; a positive odds ratio indicates a protective association with resolution of infection.

| Genetic factor | Frequency resolved *N* (%) *N = 348–352* | Frequency persistent *N* (%) *N = 681–685* | OR | 95% CI | *P* |
|---|---|---|---|---|---|
| *HLA-C1C1* | 132 (37.5) | 205 (29.9) | 1.40 | 1.07–1.84 | 0.01 |
| *HLA-C1C2* | 169 (48.0) | 342 (49.9) | 0.93 | 0.72–1.20 | 0.6 |
| *HLA-C2C2* | 51 (14.5) | 138 (20.2) | 0.67 | 0.47–0.95 | 0.02 |
| *2DL2+ HLA-C1C1* | 64 (18.2) | 121 (17.7) | 1.04 | 0.74–1.45 | 0.9 |
| *2DL3+ HLA-C1C1* | 119 (33.9) | 182 (26.7) | 1.41 | 1.06–1.86 | 0.02 |
| *2DS2+ HLA-C1C1* | 64 (18.2) | 120 (17.5) | 1.05 | 0.75–1.46 | 0.9 |
| *2DL1+ HLA-C2C2* | 50 (14.2) | 135 (19.7) | 0.68 | 0.47–0.96 | 0.03 |
| *2DS1+ HLA-C2C2* | 22 (6.3) | 32 (4.7) | 1.36 | 0.78–2.37 | 0.3 |
| *3DS1+HLA-Bw4* | 86 (24.7) | 130 (19.1) | 1.39 | 1.02–1.90 | 0.04 |
| *2DL2/2DL2+ HLA-C1C1* | 11 (3.1) | 23 (3.4) | 0.93 | 0.45–1.92 | 1.00 |
| *2DL2/2DL3+ HLA-C1C1* | 52 (14.8) | 98 (14.4) | 1.03 | 0.72–1.49 | 0.9 |
| *2DL3/2DL3+ HLA-C1C1* | 68 (19.4) | 84 (12.3) | 1.71 | 1.20–2.42 | 0.003 |
| *2DL3/2DL3+ HLA-C1C2* | 82 (23.3) | 165 (24.2) | 0.95 | 0.70–1.29 | 0.8 |
| *2DL3/2DL3+ HLA-C2C2* | 21 (6.0) | 73 (10.7) | 0.53 | 0.32–0.88 | 0.01 |

**Table 3.** Comparison of the frequencies of *HLA-C* and *KIR-HLA-C* combinations in individuals, stratified by history of transfusion of blood or plasma products. Definitions and calculations as for Table 2.

| Genetic factor | Frequency resolved *N* (%) | Frequency persistent *N* (%) | OR | 95% CI | *P* |
|---|---|---|---|---|---|
| Nontransfusion | *N* = 185–187 | *N* = 353–356 | | | |
| *HLA-C1C1* | 72 (38.5) | 93 (26.1) | 1.77 | 1.21–2.58 | 0.003 |
| *HLA-C1C2* | 85 (45.4) | 180 (50.6) | 0.81 | 0.57–1.16 | 0.3 |
| *HLA-C2C2* | 30 (16.0) | 83 (23.3) | 0.63 | 0.40–1.00 | 0.06 |
| *2DL2/2DL2+ HLA-C1C1* | 3 (1.6) | 14 (4.0) | 0.40 | 0.11–1.40 | 0.2 |
| *2DL2/2DL3+ HLA-C1C1* | 30 (16.1) | 44 (12.5) | 1.35 | 0.82–2.23 | 0.2 |
| *2DL3/2DL3+ HLA-C1C1* | 38 (20.4) | 35 (9.9) | 2.33 | 1.42–3.85 | 0.001 |
| Transfusion | *N* = 165 | *N* = 328–329 | | | |
| *HLA-C1C1* | 60 (36.3) | 112 (34.0) | 1.11 | 0.75–1.63 | 0.6 |
| *HLA-C1C2* | 84 (50.9) | 162 (49.2) | 1.07 | 0.74–1.55 | 0.8 |
| *HLA-C2C2* | 21 (12.7) | 55 (16.7) | 0.73 | 0.42–1.25 | 0.3 |
| *2DL2/2DL2+ HLA-C1C1* | 8 (4.85) | 9 (2.74) | 1.81 | 0.68–4.77 | 0.3 |
| *2DL2/2DL3+ HLA-C1C1* | 22 (13.3) | 54 (16.5) | 0.78 | 0.46–1.33 | 0.4 |
| *2DL3/2DL3+ HLA-C1C1* | 30 (18.2) | 49 (14.9) | 1.27 | 0.77–2.08 | 0.4 |

pearing to be independent of *KIR2DL3/KIR2DL3-HLA-C1C1* (Table 5). The *KIR-HLA* associations detected in HCV resolution were not affected by hepatitus B virus (HBV) infection or human immunodeficiency virus (HIV) infection [both previously associated with differential HCV recovery (*21*)], age, or sex; correspondingly, the associations were more significant in the UK cohort, which contained a lower proportion of transfused individuals.

*KIR* are clonally expressed on NK cells in a stochastic manner such that each NK cell clone expresses only a portion of the genes within the genetic profile (*2*, *22*). Thus, homozygotes for *KIR2DL3* will have more NK cells solely under the inhibitory control of *KIR2DL3* than will *KIR2DL2/KIR2DL3* heterozygotes. Similarly, individuals who have the *HLA-C1C1* genotype (and are therefore missing the HLA-C2 ligand for KIR2DL1) will have more NK cells under the inhibitory control of KIR2DL3 than individuals who have the *HLA-C1C2* genotype, in whom a proportion of NK cells will be inhibited by KIR2DL1 (an inhibitory receptor that is present in virtually all individuals). Consistent with this thesis, we observed a linear trend between the number of *KIR2DL3-HLA-C1* interactions and the odds of resolving infection ($\chi^2$ for trend = 12.33; $P = 0.0004$) (Fig. 1).

In this quantitative model, protective NK cell activity may be mediated through weak inhibitory KIR2DL3-HLA-C1 interactions (i.e., the lack of strong NK cell inhibition), perhaps in combination with one of the many nonvariable NK cell activating receptors (*23*). The protection was observed only among individuals presumably receiving low-dose HCV inocula, which suggests that the difference in the ability of distinct *KIR-HLA* genotypes to regulate NK cell activity is great enough to alter the outcome when faced with low-dose, but not high-dose, infection. The beneficial effect of lower inhibitory signals in HCV infection is consistent with other disease models in which activating interactions are advantageous against HIV disease (*9*) but disadvantageous in autoimmune disease (*8*, *10*). In light of the protection conferred by *KIR2DL3-HLA-C1* against HCV, the known conservation of the MHC-C1 motif across primate species (*24*) may indicate a selective advantage of this genotype against viral disease in general.

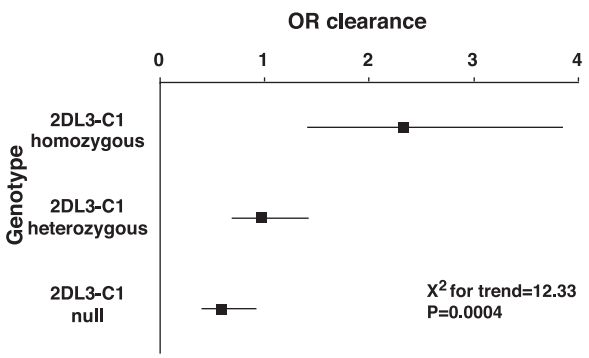


**Fig. 1.** Progressive effect of *KIR2DL3-HLA*-C1 on the outcome of HCV infection in nontransfused individuals. Individuals were divided according to *KIR2DL3* and *HLA-C* genotype. *2DL3-C1* homozygous individuals have the genotype *KIR2DL3/KIR2DL3-HLA-C1C1*; *2DL3-C1* heterozygous have the genotypes *2DL3/2DL3-C1C2*, *2DL3/2DL2-C1C1*, or *2DL3/2DL2-C1C2*; 2DL3-C1 null comprise the remainder and are missing *KIR2DL3*, *HLA-C1*, or both. The odds ratios, the 95% confidence intervals for resolution of HCV as calculated from two-by-two contingency tables, and the results of a chi-square test for trend based on the number of these interactions are shown.

**Table 4.** Frequency of *HLA-C1C1* among nontransfused individuals stratified according to *KIR2DL2* and *KIR2DL3* genotype. Definitions and calculations as for Table 2.

| *KIR* genotype | Frequency *HLA-C1C1* Resolved *N* (%) | Persistent *N* (%) | OR | 95% CI | *P* |
|---|---|---|---|---|---|
| *2DL2/2DL2* (*N* = 57) | 3 (18.6) | 14 (34.5) | 0.45 | 0.11–1.83 | 0.3 |
| *2DL2/2DL3* (*N* = 223) | 30 (36.1) | 44 (31.3) | 1.24 | 0.70–2.19 | 0.6 |
| *2DL3/2DL3* (*N* = 258) | 38 (43.7) | 35 (20.5) | 3.01 | 1.72–5.29 | 0.0001 |

**Table 5.** *HLA-C1C1* protection is present only in the context of KIR2DL3 homozygosity. Multiple variable logistic regression analyses of the effect of *KIR* and *HLA* effects in the resolution of HCV infection demonstrate that the protective effect of *HLA-C1C1* is due to its epistatic interaction with *KIR2DL3* and that this effect is present only among nontransfused individuals. Analysis was performed by stepwise logistic regression with the PROC LOGISTIC procedure (*15*), with the variables *KIR2DL3/KIR2DL3-HLA-C1C1*, *HLA-C1C1* (without *KIR2DL3/KIR2DL3*), *HLA-C2C2*, and *KIR3DS1-Bw4*.

| Group | Genotype | OR | 95% CI | *P* |
|---|---|---|---|---|
| All | *HLA-C1C1* | 1.05 | 0.73–1.50 | 0.80 |
| (*N* = 1023) | *HLA-C2C2* | 0.75 | 0.51–1.08 | 0.12 |
| | *2DL3/2DL3+ HLA-C1C1* | 1.75 | 1.21–2.55 | 0.003 |
| | *KIR3DS1-Bw4* | 1.49 | 1.09–2.04 | 0.01 |
| No transfusion | *HLA-C1C1* | 1.2 | 0.73–1.98 | 0.48 |
| (*N* = 533) | *HLA-C2C2* | 0.78 | 0.48–1.28 | 0.33 |
| | *2DL3/2DL3+ HLA-C1C1* | 2.42 | 1.42–4.13 | 0.001 |
| | *KIR3DS1-Bw4* | 1.55 | 0.99–2.41 | 0.06 |
| Transfusion | *HLA-C1C1* | 0.92 | 0.55–1.53 | 0.24 |
| (*N* = 490) | *HLA-C2C2* | 0.71 | 0.40–1.26 | 0.75 |
| | *2DL3/2DL3+ HLA-C1C1* | 1.28 | 0.75–2.18 | 0.36 |
| | *KIR3DS1-Bw4* | 1.45 | 0.93–2.26 | 0.11 |

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